Received: 30 March 2018 | Revised: 21 October 2018 | Accepted: 5 November 2018

DOI: 10.1002/ajpa.23762

WILEY Yearbook of PHYSICAL ANTHROPOLOGY

YEARBOOK OF PHYSICAL ANTHROPOLOGY ARTICLE

BDNF, endurance activity, and mechanisms underlying the evolution of hominin brains

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Funding information
National Science Foundation (BCS-1638756)

Abstract

Objectives: As a complex, polygenic trait, brain size has likely been influenced by a range of direct and indirect selection pressures for both cognitive and non-cognitive functions and capabilities. It has been hypothesized that hominin brain expansion was, in part, a correlated response to selection acting on aerobic capacity (Raichlen & Polk, 2013). According to this hypothesis, selection for aerobic capacity increased the activity of various signaling molecules, including those involved in brain growth. One key molecule is brain-derived neurotrophic factor (BDNF), a protein that regulates neuronal development, survival, and plasticity in mammals. This review updates, partially tests, and expands Raichlen and Polk's (2013) hypothesis by evaluating evidence for BDNF as a mediator of brain size.

Discussion: We contend that selection for endurance capabilities in a hot climate favored changes to muscle composition, mitochondrial dynamics and increased energy budget through pathways involving regulation of PGC-1α and MEF2 genes, both of which promote BDNF activity. In addition, the evolution of hairlessness and the skin's thermoregulatory response provide other molecular pathways that promote both BDNF activity and neurotransmitter synthesis. We discuss how these pathways contributed to the evolution of brain size and function in human evolution and propose avenues for future research. Our results support Raichlen and Polk's contention that selection for non-cognitive functions has direct mechanistic linkages to the evolution of brain size in hominins.

KEYWORDS

BDNF, brain growth, exercise, MEF2, neurotrophins, PGC-1α, thermoregulation

1 | INTRODUCTION

Humans have absolutely and relatively larger brains than do other primates and most other mammals (Stephan, Frahm, & Baron, 1981). Along with an increase in global volume, certain brain regions, notably the prefrontal cortex, underwent expansion in the human lineage (Passingham & Smaers, 2014; Smaers, Gómez-Robles, Parks, & Sherwood, 2017). The cortex accounts for 90% of the human brain, the neocortex alone 75% (Stephan et al., 1981). Because cortical growth is more protracted in humans than in other primates, the human brain is exceptionally sensitive to postnatal programming and developmental processes (Sherwood & Gómez-Robles, 2017).

The evolution of humans' unique encephalization has been explained by a range of hypotheses (e.g., Aiello & Wheeler, 1995; Dunbar, 1998; Dunbar & Shultz, 2017; Carmody & Wrangham, 2009; Navarrete, van Schaick, & Isler, 2011). While many of these hypotheses are logically compelling and bolstered by comparative data, most lack information on developmental and physiological mechanisms and are thus difficult to operationalize. One exception is the model proposed by Raichlen and Polk (2013), who suggested that selection acting on aerobic capacity upregulated particular pathways that contribute to brain growth. Besides highlighting a largely overlooked role for noncognitive factors in shaping the brain, the model's developmental emphasis is consistent with humans' protracted pattern of development. This review expands on Raichlen and Polk's (2013) model by integrating multiple sources of evidence associated with the endurance running (ER) hypothesis (Bramble & Lieberman, 2004; Carrier, 1984).

As well as having exceptionally large brains, modern humans have an exceptional capacity for locomotor endurance (Bramble &

Lieberman, 2004; Carrier, 1984). A potential evolutionary link between these two traits was first hinted at by correlational evidence in the hominin fossil record. Namely, skeletal indices of ER ability are temporally correlated with increases in absolute brain size in *Homo erectus* and *H. ergaster* (Bramble & Lieberman, 2004; Raichlen & Polk, 2013). In addition to skeletal adaptations, the evolution of hominin ER was undergirded by adaptations in metabolism (Pontzer et al., 2016), musculature (O'Neill, Umberger, Holowka, Larson, & Reiser, 2017), and skin (Jablonski, 2004; Ruxton & Wilkinson, 2011; Wheeler, 1984, 1991). Examination of these latter three adaptations within a comparative framework may yield support for a link between human endurance and encephalization.

For their initial model, Raichlen and Polk (2013) marshaled three main lines of evidence. First, measures of aerobic fitness are positively correlated with regional brain volumes in humans and other mammals across lifespan (Chaddock, Erickson, Prakash, Kim, et al., 2010; Chaddock, Erickson, Prakash, Vanpatter, et al., 2010; Chappell, Garland, Robertson, & Saltzman, 2007; Erickson et al., 2011; Peters et al., 2009). Second, brain size is positively associated with a measure of aerobic capacity ($VO_{2\ max}$) in a broad sample of mammals (Raichlen & Gordon, 2011). Third, independent experiments in rodents have shown that selection for exercise-related traits modifies both the body and brain. In mice, selective breeding for voluntary wheel-running brings about increases in the size of certain brain regions (Kolb et al., 2013) and changes in various neurotransmitter pathways (Rhodes, Gammie, & Garland, 2005). Similarly, rats selectively bred for high $VO_{2\ max}$ exhibit a pro-endurance muscular phenotype (Howlett et al., 2003; Ren et al., 2016), gains in cognitive abilities (Wikgren et al., 2012), and a more pronounced genomic response in the brain to physical activity (Bye et al., 2008).

The interactions between endurance physiology and brain growth are increasingly well understood. Mediators that have received special attention include generalized growth factors, such as insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor (VEGF), and relatively specialized factors such as brain-derived neurotrophic factor (BDNF) (Colcombe et al., 2006; Cotman, Berchtold, & Christie, 2007; Erickson et al., 2011; see below). In Raichlen and Polk's (2013) model, selection for increased aerobic capacity entailed an upregulation of growth factors, especially BDNF, that concomitantly promoted brain growth (Figure 1a). Importantly, by implicating intrinsic changes in growth factor regulation, this model does not require activity during ontogeny.

The goal of this article is to identify and tie multiple physiological mechanisms into a more elaborate, integrative model linking endurance capacity to encephalization in humans. We begin with a detailed review of the diverse biological roles of BDNF in the body and brain and point to current issues of individual variation in BDNF and measurement. We then explore how other changes in muscle biology, energy production, and integumentary systems, which likely resulted from selection for endurance capability in hot climates, also act to promote BDNF activity. Finally, we place the results of this review into the context of an evolutionary model that illustrates how resulting changes in energy budgets can promote BDNF activity and brain growth throughout development. While this review focuses on BDNF, we acknowledge the importance of other factors and pathways for further investigation (Bye et al., 2008; Cotman et al., 2007).

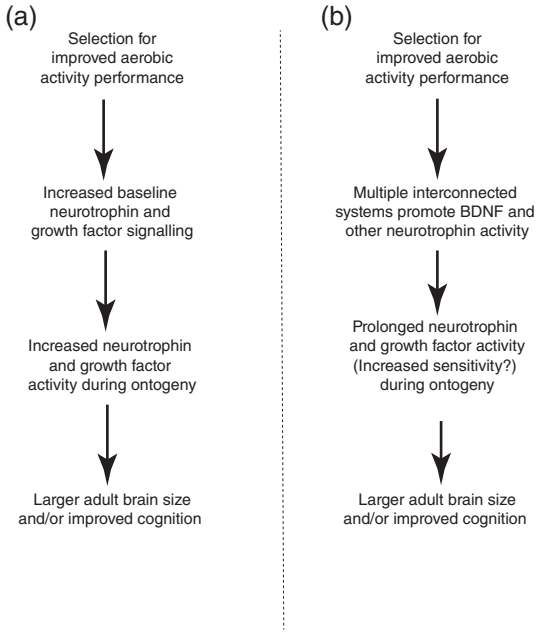

FIGURE 1 (a) Developmental model (following Raichlen & Polk, 2013) suggesting that selection favoring aerobic activity led to increased baseline levels of BDNF and other neurotrophins during development. (b) The model proposed in this review where selection for endurance activity has led to multiple interdependent mechanisms that regulate levels and duration of expression of BDNF and other growth factors, leading to increased hominin brain size

2 | BDNF BIOLOGY

2.1 | Introduction

BDNF is of special interest for two broad reasons. First, BDNF is the key regulator of vertebrate neural growth from prenatal through preadolescent periods (Lipsky & Marini, 2007). Second, the stimulation of BDNF by physical activity in humans and other mammals indicates an intimate relationship between BDNF regulation and underlying exercise physiology (Dinoff, Herrmann, Swardfager, & Lanctôt, 2017; Neeper, Gómez-Pinilla, Choi, & Cotman, 1995). Thus, to explore in detail whether BDNF could have mediated brain enlargement in hominin evolution, here we review some of the basic biology underlying BDNF function.

BDNF is a 119-amino acid protein that is created upon the cleavage of its precursor, proBDNF (Jones & Reichardt, 1990). BDNF and its primary receptor, tyrosine kinase receptor B (TrkB), are found throughout the nervous system but are especially concentrated in the cortex and hippocampus (Webster, Herman, Kleinman, & Shannon Weickert, 2006). During early stages of embryonic development, BDNF–TrkB signaling promotes the differentiation of cortical progenitor cells (CPC) and later promotes CPCs' differentiation into neurons (i.e., neurogenesis) (Bartkowska, Paquin, Gauthier, Kaplan, & Miller, 2007). In the postnatal neocortex, BDNF signaling is required for maintaining dendritic and somatic volume (Gorski, Zeiler, Tamowski, &

Jones, 2003). BDNF also supports long-term memory by stimulating new dendrites, synapses, and neurons to form in the hippocampus throughout lifespan (Bekinschtein et al., 2007; Waterhouse et al., 2012). More generally, BDNF may promote growth by increasing basal protein synthesis rates in cortical neurons (Takei et al., 2009). proBDNF is also neuroactive, having a high affinity for an apoptosis-signaling receptor ($p75^{NTR}$), and may mediate synaptic pruning in the prenatal brain (Deinhardt & Chao, 2014).

Along with the brain, other tissues express BDNF. Levels of BDNF protein are in fact higher in some visceral epithelia (e.g., lung, colon, and bladder) than in the brain, possibly to modulate connections with peripheral neurons (Lommatzsch et al., 1999). In addition, vascular endothelial cells secrete BDNF in response to fluid shear stress and hypoxic conditions (Nakahashi et al., 2000; Wang, Ward, Boswell, & Katz, 2006). The influence of these nonneuronal BDNF sources on brain development is not well understood.

BDNF also has important roles in energy metabolism. In promoting growth and survival, BDNF–TrkB activity necessarily increases energy production within a cell. For example, in developing cortical neurons, BDNF was shown to increase glucose utilization and glucose transporter 3 expression (Burkhalter, Fiumelli, Allam, Chatton, & Martin, 2003) and to improve mitochondrial efficiency (Markham, Cameron, Franklin, & Spedding, 2004). In addition to its local effects, BDNF modulates systemic energy homeostasis via central nervous system (CNS) pathways. Centrally administered BDNF reduces glucose production by the liver (Meek et al., 2013) and increases glucose uptake in peripheral tissue (see Marosi & Mattson, 2014, for review). In contrast, suppression of BDNF in the brain causes obesity, diabetes, and disordered feeding behavior in mice (Marosi & Mattson, 2014).

The *BDNF* gene is highly conserved in vertebrates (Tettamanti et al., 2010). However, the mammalian *BDNF* locus is uniquely characterized by a high ratio of nonsynonymous to synonymous substitutions ($\omega = 1.06$) (Tettamanti et al., 2010). As ω values greater than 1 are considered evidence for positive selection on a genetic site (Yang & Bielawski, 2000), mutations in the *BDNF* locus possibly played a role in the evolution of mammalian neurobiology. Whether there has been similar positive selection among mammalian clades or within Primates is the subject of ongoing research.

In terms of number of exons, promoters, and alternative transcripts, the human *BDNF* locus is more complex than that of mice and rats (Pruunsild, Kazantseval, Aid, Palm, & Timmusk, 2007). Whether nonhuman primates have the same transcriptional complexity in *BDNF* is uncertain. Although the coding sequence of chimpanzee and human *BDNF* differs by only four base pairs (Tettamanti et al., 2010), thorough comparative analyses of the locus have not been published.

Several polymorphisms (SNPs) have been identified in the human *BDNF* locus (Petryshen et al., 2010). The SNP that has received the most attention is Val66Met, which resulted from an A-to-G substitution in the ancestral gene. While Val66Met does not alter the final protein product, the mutation is physiologically significant in that Met-carrying neurons show reduced secretion and intracellular transport of mature BDNF *in vitro* (Egan et al., 2003). Positive selection on the *BDNF* locus was reported in a global population-genetics study, with strongest evidence of selection found to have acted on the Val allele in European samples (Petryshen et al., 2010). The functional consequences of *BDNF* that made it a target of selection in recent human evolution have not yet been defined. In keeping with the model advanced in this article, we propose that *BDNF*'s metabolic effects (rather than any concomitant neurocognitive effects) are a plausible target of selection for endurance capability.

BDNF gene expression changes in multiple ways throughout mammalian development. In the human dorsolateral prefrontal cortex, BDNF protein levels peak in infancy, drop slightly in toddlerhood, and then plateau through young adulthood (Wong, Webster, Cassano, & Weickert, 2009). *BDNF* alternative transcripts are also differentially expressed throughout ontogeny, with transcriptional dynamism peaking in the first approximately 10 years of life when the brain is most plastic (Wong et al., 2009). The laminar and temporal expression patterns of *BDNF* transcripts differ between rats and humans (Sathanoori et al., 2004), admitting of a role for *BDNF* expression in these species' neurobiological differences. Of prime importance to this review, Liu et al. (2012) provide ontogenetic comparative data that distinguish *BDNF* mRNA expression levels among chimpanzees, humans, and macaques. Their results (Figure 2) run counter to Raichlen and Polk's (2013) prediction that humans would have relatively increased peak levels of *BDNF* mRNA; instead, humans show prolonged peak *BDNF* expression, lasting through adolescence, relative to the other primates (Liu et al., 2012). Curiously, the different expression patterns (Liu et al., 2012) correspond to these species' different developmental trajectories in gross brain morphology (Leigh, 2004, 2012).

2.2 | BDNF and brain volume

While the role of BDNF in influencing brain structure and function is well established, ongoing research seeks to define the functional and structural consequences of invasive BDNF manipulation in animals and of *BDNF* variants in humans. Efforts are also underway to evaluate correlations between circulating BDNF levels and brain volumes.

Gene knockout (KO) studies indicate that BDNF significantly influences brain volume. Germline *Bdnf*-KO mice are characterized by smaller ganglia and lower cell counts in the cortex and hippocampus (Ernfors, Lee, & Jaenisch, 1994; Jones, Fariñas, Backus, & Reichardt, 1994). Because these mice have a reduced lifespan, their adult brain volume cannot be compared with wildtype. However, brain-specific

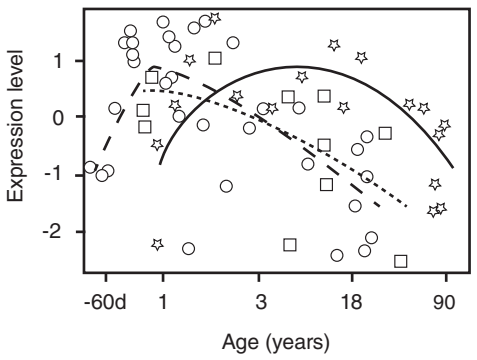

FIGURE 2 Expression of *BDNF* across the lifespan in humans, chimpanzees, and macaques. Humans: Solid line and stars; chimpanzee: Dotted line and squares; macaque: Dashed line and circles. Adapted from Liu et al. (2012)

Bdnf-KO mice have a normal lifespan, and their adult brain mass is reduced by approximately 10% compared with wildtype (Chang, Khare, Dani, Nelson, & Jaenisch, 2006). In forebrain-specific *Bdnf*-KO mice, the neocortex is thinner at maturity, likely due to a reduction in postnatal neuronal survival (Gorski et al., 2003). We conjecture that such manipulations would, hypothetically, have a greater effect on brain size in humans given the prolonged pattern of *BDNF* expression (Liu et al., 2012).

Other studies have investigated BDNF's role in embryonic stages of brain growth. For example, the proliferation of CPCs can be reduced by suppressing BDNF with antibodies (Barnabé-Heider & Miller, 2003) and by genetic knockdown of *trkB* (Bartkowska et al., 2007). Conversely, BDNF overexpression in the telencephalon increases neurogenesis and CPC proliferation (Bartkowska et al., 2007). Whether germline overexpression of *BDNF* (e.g., by gene duplication) is sufficient to increase adult brain volume has not yet been tested.

Numerous magnetic resonance imaging studies have looked for morphometric associations with the Val66Met polymorphism. Two meta-analyses found no correlation between Val66Met and hippocampal volume in adults (Harrisberger et al., 2014; Kim et al., 2015). However, a study in middle-aged subjects (n = 330) found that the Met allele was positively correlated with gray-matter volume in parts of the frontal gyrus, temporal gyrus, and cerebellum (Liu, Huang, et al., 2014). In young adults (n = 308), Met was correlated with greater surface area of the insular cortex (Wang et al., 2014). In children and early adolescents, Met has been correlated with greater surface area in the parietal and prefrontal cortices as well as greater cortical thickness in occipital and parietal regions (n = 499 [De Araujo et al., 2018]; n = 185 [Hashimoto et al., 2016]; n = 78 [Jasińska et al., 2017]). The observed differences may result from a compensatory mechanism by which Met-carrying neurons upregulate and secrete more proBDNF, which is cleaved extracellularly to promote gray matter survival (Hashimoto et al., 2016). Although the genotype–phenotype relationship remains poorly understood, the mounting evidence from large, geographically diverse samples suggests that mutations in *BDNF* appreciably affect regional brain volumes in humans. By extension, factors that influence *BDNF* expression might also lead to changes in brain volume.

Additional evidence comes from associations between basal serum BDNF levels and regional brain volumes. For example, gray-matter volume was significantly correlated with serum BDNF in healthy adults (n = 17 [Poletti et al., 2017]; n = 32 [Zugman et al., 2015]). In an adolescent sample (n = 23), amygdala volume was correlated with serum BDNF (Inal-Emiroglu et al., 2015). Although consistent with a link between higher BDNF levels and increased brain growth, these studies are limited by relatively small sample sizes. Longitudinal studies tracking both brain volume and peripheral BDNF across development have not been published.

2.3 | Measurement of BDNF

Evaluating the ontogenetic role of differential BDNF regulation (or that of other factors not spotlighted here) is important for assessing a link between endurance and the brain in human evolution. Ideally, for example, a longitudinal study might compare BDNF levels among primate species. However, such comparisons are not simple to conduct.

BDNF protein is commonly quantified by enzyme-linked immunosorbent assay (ELISA) and *BDNF* mRNA by in situ hybridization. These methods have been used to measure BDNF protein (Sheldrick, Camara, Ilieva, Riederer, & Michel, 2017) and mRNA (Wong et al., 2009) levels in postmortem human brains. Cerebrospinal fluid also contains relatively minute quantities of BDNF but is seldom sampled in living humans for such experimental aims as pertain to this review (Laske et al., 2007; Pillai et al., 2012).

The most comment source for sampling BDNF in living animals is peripheral blood. Whole blood and its components (serum, plasma, and platelets) each yield markedly different concentrations (Lommatzsch et al., 2005; Radka, Hoist, Fritsche, & Altar, 1996). Serum, for example, yields up to approximately 200-fold more BDNF than does plasma (Lommatzsch et al., 2005).

Measurement and interpretation of peripheral BDNF are complicated by a number of individual factors. For example, BDNF levels in plasma—but not in platelets or whole blood—are negatively correlated with age and weight (Lommatzsch et al., 2005). BDNF levels, as well as which blood component contains the most BDNF, vary by gender (Lommatzsch et al., 2005; Trajkovska et al., 2007). Gender also appears to influence patterns of diurnal variation in BDNF levels. In men, plasma BDNF has been found to peak in the morning and fall throughout the day, while women's serum BDNF remains stable and similar to men's nighttime levels (Begliuomini et al., 2008; Choi, Bhang, & Ahn, 2011; Piccinni et al., 2008). Additionally, plasma BDNF levels were lower in postmenopausal than in fertile ovulatory women, a potentially neglected factor in studies of older adults (Pluchino et al., 2009).

Correlations between levels of BDNF in blood and the CNS are not simple. The blood component in which BDNF levels are best correlated with brain levels varies across species. For example, hippocampal BDNF levels were best reflected in whole blood in rats but in plasma in pigs (Klein et al., 2011). In mice, peripheral BDNF is undetectable (Klein et al., 2011; Radka et al., 1996), making a brain–periphery relationship difficult to establish in experimental models.

2.4 | BDNF and physical activity

Decades of research have demonstrated the benefits of exercise for the brain, including gains in regional brain volumes and corresponding gains in cognition (Hillman, Erickson, & Kramer, 2008; Hötting & Röder, 2013). BDNF is a key mediator of these effects. The interactions of physical activity, BDNF, and brain size, from both developmental and evolutionary perspectives, must be evaluated to test Raichlen and Polk's (2013) hypothesis.

Artificial selection for exercise behaviors brings about heritable changes in brain structure and function. Notably, whole-brain mass and midbrain volume are increased in mice selectively bred for high levels of voluntary wheel running (HR mice) (the authors did not report BDNF levels) (Kolb et al., 2013). In a similar experiment, HR mice had larger exercise-induced increases in hippocampal BDNF, suggesting a correlated change in the regulation of BDNF signaling

(Johnson, Rhodes, Jeffrey, Garland, & Mitchell, 2003). Other experiments have selectively bred rats for innately (i.e., exercise-independent) high $VO_{2\ max}$. Compared with controls, high-$VO_{2\ max}$ rats show several muscular changes conducive to endurance activity (e.g., increases in capillary density, oxygen conductance, and transcripts associated with mitochondrial function) (Howlett et al., 2003; Ren et al., 2016) and a more pronounced genomic response to exercise in the brain to exercise (Bye et al., 2008). Further, high-$VO_{2\ max}$ rats perform better in tests of learning and memory, regardless of exercise experience (Sarga et al., 2013; Wikgren et al., 2012). Taken together, these results imply that some of the alleles associated with physical activity can act pleiotropically to alter brain structure and function, in both activity-dependent and -independent manners.

The effects of short- and long-term exercise on BDNF levels have been studied repeatedly. Acute exercise in the form of single bouts has been shown to increase peripheral BDNF levels in humans (e.g., Rasmussen et al., 2009; Saucedo Marquez, Vanaudenaerde, Troosters, & Wenderoth, 2015). A meta-analysis of 55 acute-exercise studies in healthy adults confirmed this effect, noting that exercise duration was correlated with larger increases in BDNF (Dinoff et al., 2017). Curiously, a significant correlation between acute exercise and BDNF levels in women was not reported (Dinoff et al., 2017), similar to another meta-analysis in which effect sizes were found to be significant but smaller in women (Szuhany, Bugatti, & Otto, 2015).

Studies on the effects of long-term exercise interventions on peripheral BDNF have reported mixed results (Heisz et al., 2017). In one meta-analysis, 3 out of 10 included studies reported lasting training-induced increases in basal BDNF levels (mean duration and effect size were not specified) (Knaepen, Goekint, Heyman, & Meeusen, 2010). A more recent meta-analysis of 29 studies found similarly modest but significant effects (Dinoff et al., 2016). Unlike acute exercise, long-term exercise was not associated with significant effect-size differences based on gender or measurements in plasma versus serum (Dinoff et al., 2016).

Although exercise interventions increase peripheral BDNF levels, cross-sectional studies have found an inverse correlation between average physical-activity levels and basal serum BDNF levels (Babaei, Damirchi, Mehdipoor, & Tehrani, 2014; Currie, Ramsbottom, Ludlow, Nevill, & Gilder, 2009; Nofuji et al., 2008). Likewise, basal serum BDNF levels were inversely correlated with $VO_{2\ max}$ (Babaei et al., 2014; Cho et al., 2012; Currie et al., 2009). This finding is not well understood but may reflect a positive correlation between platelet count and both $VO_{2\ max}$ and physical activity levels (Currie et al., 2009). Because platelets absorb and store BDNF (Yamamoto & Gurney, 1990), it is plausible that higher platelet counts would reduce the BDNF measured in other blood components (see Walsh & Tschakovsky, 2018, for review).

We include this section on exercise-mediated effects to be thorough in our review of how BDNF can be regulated. We emphasize elsewhere that our model does not require higher levels of exercise during development for humans. Nevertheless, exercise effects on BDNF during one's lifetime explain some interindividual variation in brain function and regional brain volumes (e.g., Chaddock , Erickson, Prakash, Kim, et al., 2010; Chaddock, Erickson, Prakash, Vanpatter, et al., 2010).

2.5 | Mechanisms affecting peripheral BDNF and brain-tissue BDNF

The sources of exercise-induced increases in peripheral BDNF are debated. However, the brain is widely assumed to be the main contributor. Based on the arterial–internal jugular venous difference in BDNF concentration, the brain was estimated to produce as much as 80% of the peripheral BDNF increase in humans after exercise (Rasmussen et al., 2009).

Peripheral sources of exercise-induced BDNF have not been confirmed *in vivo*, although there are compelling candidates. As noted earlier, platelets store BDNF and release it in response to various agonists (Fujimura et al., 2002; Yamamoto & Gurney, 1990). At least three of these agonists (thrombin, fluid shear stress, and calcium) are increased by aerobic exercise (Hyers, Martin, Pratt, Dreisin, & Franks, 1980; Ikagugi et al., 2003; Ljunghall et al., 1984). Other candidate sources for peripheral BDNF are vascular endothelial cells, which secrete BDNF in response to hypoxic stress *in vitro* (Wang, Ward, et al., 2006) and perhaps to local hypoxia during exercise *in vivo*. Because peripherally injected BNDF readily crosses the blood–brain barrier (Pan, Banks, Fasold, Bluth, & Kastin, 1998), endogenous BDNF from peripheral sources can likely enter the brain as well. However, the extent or significance of this effect has yet to be determined.

Thus far, two mechanisms linking physical activity to BDNF upregulation in the brain have been identified. One mechanism involves the production of ketones for energy, which occurs as glucose stores are depleted during vigorous and/or prolonged exercise. Levels of the ketone β-hydroxybutyrate strongly correlate with *Bdnf* upregulation in the mouse hippocampus after voluntary exercise (Marosi et al., 2016). This finding is supported by *in vitro* evidence that β-hydroxybutyrate induces *Bdnf* in cortical neurons (Marosi et al., 2016; Sleiman et al., 2016). Another mechanism involves FNDC5, a protein that is upregulated to similar levels in both muscle cells and neurons after exercise in mice (Wrann et al., 2013). Together with peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) and other transcription factors, FNDC5 stimulates BDNF production in cultured hippocampal neurons (Wrann et al., 2013). Peripherally delivered FNDC5 was correlated with increased BDNF levels in the hippocampus, suggesting that FNDC5 crosses the blood–brain barrier and is sufficient to upregulate BDNF in the brain (Wrann et al., 2013). To what extent endogenous peripheral FNDC5 can induce BDNF in the brain is unknown.

As evidenced by multiple studies in children and adolescents, variation in aerobic capacity and exercise during ontogeny accounts for a significant (though, to be clear, not dramatic) amount of interindividual variation in brain size and cognitive outcomes (e.g., Kao, Westfall, Parks, Pontifex, & Hillman, 2017; Whiteman, Young, Budson, Stern, & Schon, 2016). While activity during ontogeny almost certainly cannot account for the interspecific patterns noted above, the differential responsiveness of the brain to exercise has not been explicitly tested. To place this model effectively in evolutionary context, we emphasize that selection for endurance capacity has led to prolonged levels of high BDNF expression that, in turn, have consequences for prolonged brain growth.

3 | PROMOTERS OF BDNF FROM MUSCULAR, METABOLIC, AND INTEGUMENTARY SYSTEMS

The evolution of endurance running capacity has affected multiple physiological systems in the hominin body. Notable pro-endurance adaptations are evident in human skeletal muscle. Compared to chimpanzees, humans have a markedly high ratio of slow-twitch (ST) to fast-twitch skeletal myofibers (O'Neill et al., 2017), a phenotype that confers better performance in aerobically demanding exercise (Coyle, Sibossis, Horowitz, & Beltz, 1992). Humans also have a raised energy budget (among other metabolic alterations) relative to nonhuman primates (Pontzer et al., 2016). Finally, humans have a suite of integumentary adaptations, including hairlessness, which enhance thermoregulation during endurance activity (Carrier, 1984; Ruxton & Wilkinson, 2011; Wheeler, 1984, 1991). At first glance, changes in muscular, metabolic, and integumentary systems may not appear related to neurocognitive evolution in humans. However, there are molecular pathways in each system that may significantly influence the brain, in part via interaction with BDNF. In this section, we provide preliminary descriptions of these pathways.

3.1 | Muscular and metabolic systems

We highlight two genetic factors that regulate muscle development and function as well as interact with the brain through BDNF-dependent mechanisms. These are myocyte-enhancer factor 2 (MEF2) and PGC-1α. Their roles in endurance and the brain are summarized in Figure 3.

3.1.1 | MEF2

MEF2 is a family of transcription factors (MEF2A–D) best known for their role in muscle development and maintenance (Black & Olson, 1998). The isoforms activate different, though overlapping, sets of genes in the various muscle tissues (Estrella et al., 2015). In particular, MEF2A is necessary for myoblast differentiation in skeletal muscle (Estrella et al., 2015). At later stages, MEF2A is among the transcription factors that drive ST fiber formation (Potthoff et al., 2007).

MEF2 proteins are also expressed in the mammalian brain (Leifer, Golden, & Kowall, 1994; Lyons, Micales, Schwarz, Martin, & Olson, 1995). In humans, MEF2C is highly expressed in the cortex and cerebellum with a temporal pattern that suggests a role in differentiating cortical neurons (Leifer et al., 1994). In mice, conditional knockout of MEF2C in neural progenitor cells impaired differentiation, leading to reductions in both cell-body and whole-brain volume (Li et al., 2008). In the postnatal cerebrum, MEF2A, C, and D modulate activity-dependent synaptic plasticity in the hippocampus (Barbosa et al., 2008; Cole et al., 2012). It is also worth noting that along with neurological impairments, conditional knockout of MEF2C in the neural crest leads to a range of craniofacial deformities in mice (Verzi et al., 2007). MEF2 transcription factors thus appear to influence brain growth at multiple levels, from the regulation of neural progenitor cells to global effects on the braincase.

Particularly pertinent to this article, some of MEF2's neural functions are interdependent with BDNF. BDNF's cell-survival signal depends on MEF2C and MEF2A in developing cortical and granule neurons, respectively (Liu et al., 2003; Shalizi et al., 2003). MEF2A is also a probable upregulator of BDNF by binding to a nearby promotor, and BDNF promotes MEF2A in a positive feedback loop (Liu et al., 2012). Peak expression of MEF2A shows a similar pattern to BDNF (Figure 2), and both show prolonged expression in humans relative to that in chimpanzees and macaques (Liu et al., 2012). Liu et al. (2012) also point out that this effect may have occurred later in human evolution because the gene structure appears to have diverged from the last common ancestor shared by humans and Neanderthals.

3.1.2 | PGC-1α

The second pathway relating muscle and metabolism to brain function involves PCG-1α. The encoding gene, *PPARGC1A*, is considered a

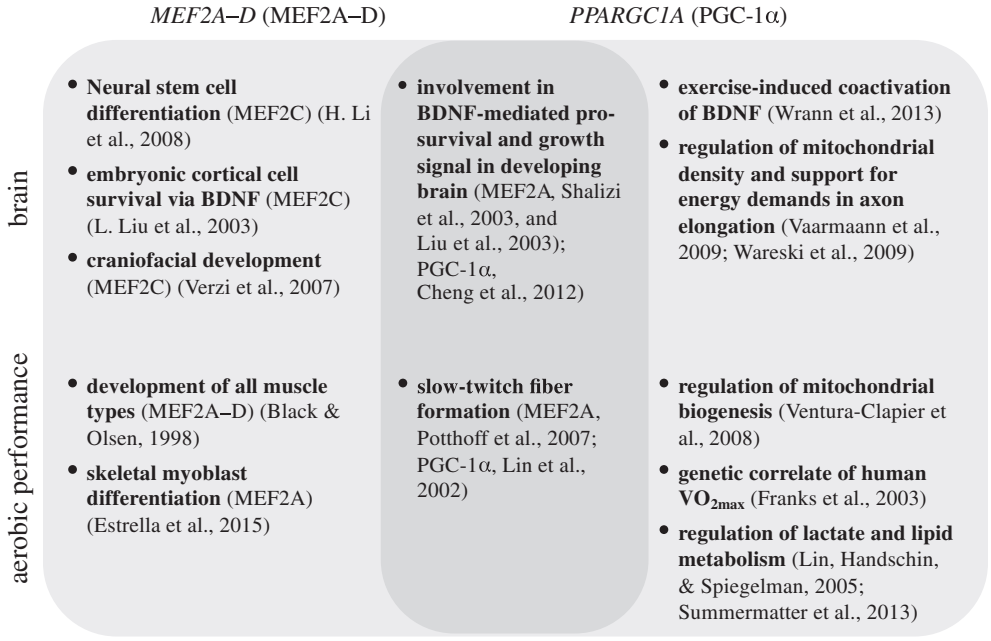

FIGURE 3 Venn diagram illustrating the links between *PPARGC1A* and *MEF2*, and their effects on aerobic performance variables and the brain

"human accelerated region" due to its high degree of divergence from the corresponding region in chimpanzees (Pollard et al., 2006). PCG-1α is a coactivator of multiple genes that control mitochondrial biogenesis, glucose and lipid homeostasis, and a range of other metabolic processes (Lin, Handschin, & Spiegelman, 2005). Relevant to this review, PCG-1α drives the development of ST fibers in skeletal muscle via coactivation with MEF2 transcription factors (Handschin, Rhee, Lin, Tarr, & Spiegelman, 2003; Lin et al., 2002). It also mediates experience-dependent adaptations in skeletal muscle. Notably, endurance exercise leads to PCG-1α upregulation in human muscle (Barrès et al., 2012; Pilegaard et al., 2003), where the coactivator promotes efficient use of lactate as an energy source (Summermatter et al., 2013). Consistent with its roles at the level of cell and tissue, PGC-1α influences systemic measures of endurance. In mice, PGC-1α overexpression led to gains in innate $VO_{2\ max}$ and exercise capacity (Tadaishi et al., 2011). This finding is corroborated by human studies showing correlations between *PPARGC1A* SNPs and $VO_{2\ max}$ (Franks et al., 2003; He et al., 2008; Lucia et al., 2005; Nishida et al., 2015).

Given its myriad metabolic roles, PGC-1α also influences brain development and function. As noted above, PGC-1α links exercise to cerebral BDNF upregulation (Wrann et al., 2013). PGC-1α has also been found to regulate mitochondrial density in neurons (Wareski et al., 2009), and BDNF's ability to increase mitochondrial count depends on PGC-1α (Cheng et al., 2012). Overexpression of PGC-1α leads to an increase in dendritic spines and synaptic differentiation markers (Cheng et al., 2012) and to acceleration of axon elongation *in vitro* (Vaarmann et al., 2016), raising the possibility that changes in PGC-1α activity patterns may influence developmental trajectories in the brain.

Evidence that *PPARGC1A* has undergone exceptional mutation in the human lineage, together with evidence for PGC-1α's roles in metabolism and ST fiber development, suggests that this gene may have been altered by selection for endurance capacity. Changes in *PPARGC1A* may thus help to explain differences in aerobic capacity and muscle composition between humans and chimpanzees (cf., O'Neill et al., 2017; Pontzer et al., 2016; Sockol et al., 2007). Further, any correlated changes in PGC-1α's neurodevelopmental effects have implications for interspecific differences in the brain.

3.2 | Integumentary system

A key component of the endurance running hypothesis involves humans' ability to better rid their bodies of the excess heat generated during endurance activity in a hot climate (Bramble & Lieberman, 2004; Carrier, 1984; Ruxton & Wilkinson, 2011; Wheeler, 1984, 1991). Several mechanisms support this human ability, including the evolution of hairless skin to enhance evaporative sweating (Carrier, 1984; Wheeler 1984, 1991; Jablonski, 2004). Beneath the skin, excess heat is brought to the periphery through a cutaneous vasodilatory response (CVR; Figure 4). This response is complex and is mediated by a number of factors (see Kellogg, 2006, for review). A principal vasodilator is nitric oxide (NO), which is produced by NO synthases (NOS) in skin and sympathetic nerve terminals in response to locally and internally sensed heat, respectively (Kellogg, Zhao, & Wu, 2009; Mills et al., 1997). During exercise in a hot environment, the CVR plateaus

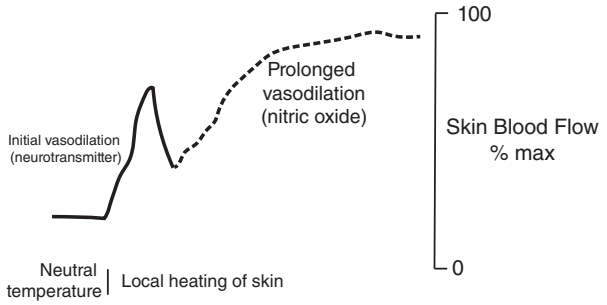

FIGURE 4 Cutaneous vasodilatory response results initially from sympathetic neurotransmitter function, and with increasing temperature relies more heavily on nitric oxide generated from UV exposure in the skin (adapted from Johnson and Kellogg, 2010)

far below its maximum, probably due to inhibition by baroreceptor signals (Brengelmann, Johnson, Hermansen, & Rowell, 1977; Kellogg, Johnson, Kenney, Pérgola, & Kosiba, 1993). Yet, hairless humans have a way to generate nitric oxide that is independent of NOS and thus not subject to this inhibition. When exposed to ultraviolet radiation (UV), nitrogen-containing compounds in the skin yield large amounts of NO via photolysis (Liu, Fernandez, et al., 2014; Mowbray et al., 2009; Paunel et al., 2005). This NO enters circulation and increases arterial dilation (Liu, Fernandez, et al., 2014), thereby alleviating some of the heat-stress-related reductions in CVR.

The consequences of NO production in the skin have potential implications for cognitive development. Nitric oxide acts as a neurotransmitter/modulator in a broad variety of contexts, including synaptic plasticity, neuroendocrine function, and neurovascular homeostasis (Calabrese et al., 2007; Guix, Uribesalgo, Coma, & Muñoz, 2005). Some of its functions are interdependent with BDNF. In cultured neural stem cells, a BDNF–NO positive feedback loop was shown to regulate proliferation and differentiation (Cheng, Wang, Cai, Rao, & Mattson, 2003). In slices of rat brain, application of a NO donor induces BDNF (Banoujaafar et al., 2016). In mouse models of stroke, NOS has been shown to facilitate neurogenesis (Chen et al., 2005) white matter changes (Cui et al., 2013), and neuroprotection (Li et al., 2014) by upregulating BNDF. Furthermore, there is evidence that exercise stimulates endothelial NOS-dependent BDNF expression in cerebrovascular endothelia (Monnier et al., 2017).

Whether NO upregulation of BDNF assists in normal brain growth is not currently known. As a highly reactive and short-lived molecule, NO is difficult to study directly in the brain (Wang, Paton, & Kasparov, 2006). However, indirect evidence suggests that NO can enter peripheral circulation and persist long enough to reach the CNS. That is, in mice, inhalation of NO improves stroke outcome (Li, Shemmer, Stone, Nardi, & Quartermain, 2013; Pham et al., 2015).

In addition to NO, UV rays induce the synthesis of other molecules (Jablonksi, 2004) that may affect the brain. A recently discovered pathway links UV exposure in bare skin to an increase in circulating urocanic acid (Zhu et al., 2018). This molecule was found to enter the CNS and increase the synthesis and release of glutamate (the principal excitatory neurotransmitter), which corresponded to improvements in spatial and motor memory in mice (Zhu et al., 2018). While the effects of skin-derived neuromodulators have received relatively little attention in animal and human research, we believe that

future research can evaluate hypotheses linking the evolution of human skin to changes in neurobiology. The fact that NO responds to exercise and sunlight and is associated with neurogenesis provides some support for a mechanistic connection between hairlessness and the potential for improvements in neural function and perhaps brain growth.

4 | DISCUSSION

The results of this review reveal several important findings. Most importantly, the role for BDNF in brain growth and maintenance is well documented and justifies continued research on the protein's significance in human brain evolution. Selection has acted on *BDNF* during vertebrate evolution, and changes in the genetic structure (and related function) may have contributed to the differences in brain size between mammals and other vertebrates (Tettamanti et al., 2010). Whether selection has further modified *BDNF*'s sequence within mammals known to have relatively large brains (e.g., Primates) remains to be tested. Liu et al. (2012) demonstrate that peak expression of BDNF and MEF2 are prolonged across the human lifespan, in comparison to chimpanzees and macaques, and this difference matches known differences in the patterns of postnatal brain growth among these species. Considering these different interspecific patterns, we revise Raichlen and Polk's (2013) hypothesis to implicate the prolongation of peak BDNF levels, rather than greater peak levels, in human brain enlargement.

The second major finding of this review is that the regulatory framework for BDNF is influenced by functional elements of the muscular, metabolic, and integumentary systems (Figures 5 and 6), which are known to be related to endurance activity and have changed substantially during human evolution (Carrier, 1984; Jablonski 2004; O'Neill et al., 2017; Ruxton & Wilkinson, 2011; Wheeler, 1984, 1991). In muscular and metabolic systems, two genes (*MEF2* and *PPARGC1A*) involved in various pro-endurance processes (e.g., slow-twitch fiber production, mitochondrial dynamics, and glucose metabolism) are also involved in regulation of BDNF. Evidence for when these changes occurred in human evolution is not fully resolved. *MEF2A* is believed to have mutated in humans after the divergence of humans and neanderthals from their common ancestor (Liu et al., 2012). While human *PPARGC1A* has significant differences from that of chimpanzees, the possible timing of this mutation has not been reported. In the skin, the evolution of hairlessness not only represents a precondition for a larger, more thermogenic brain in the hot ancestral climate (Bramble & Lieberman, 2004; Wheeler, 1984, 1991) but also enables greater neuromodulation by UV radiation. The resulting increase in UV-induced production of NO and glutamate (among, we expect, other pathways not reviewed here or yet discovered) has consequences for plasticity in the brain.

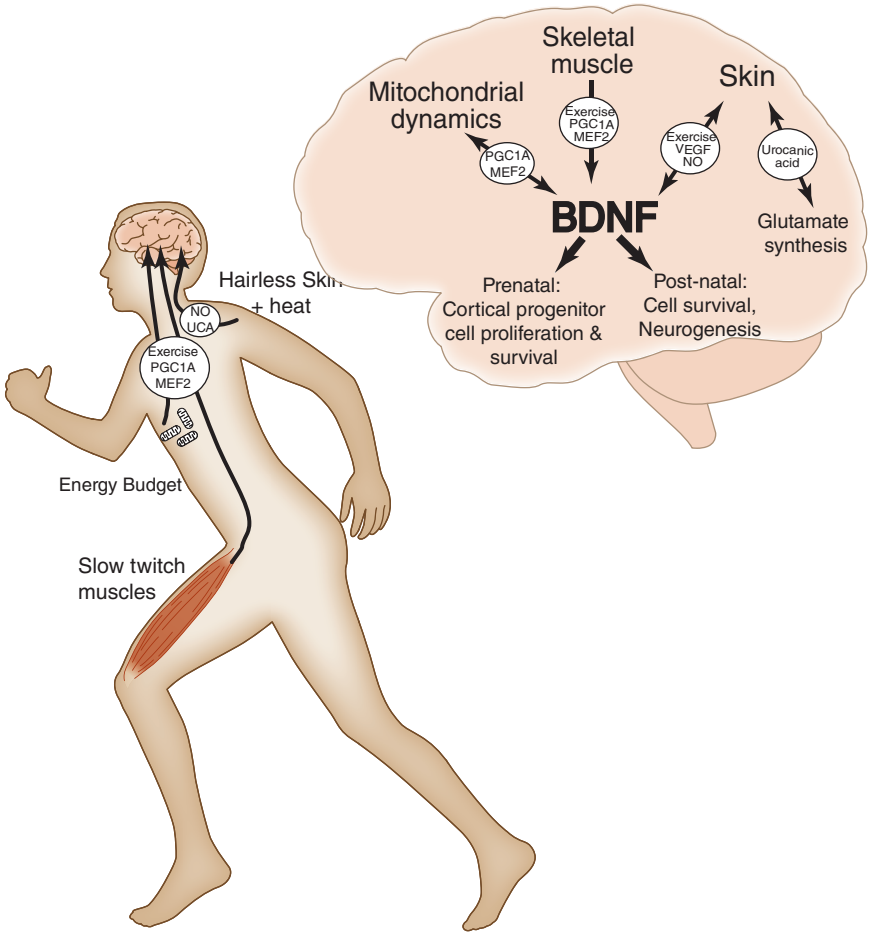

FIGURE 5 Selection for endurance activity in a hot climate has promoted changes to muscular, energetic and integumentary systems that act to promote BDNF and glutamate leading to differential brain size in humans relative to early hominins

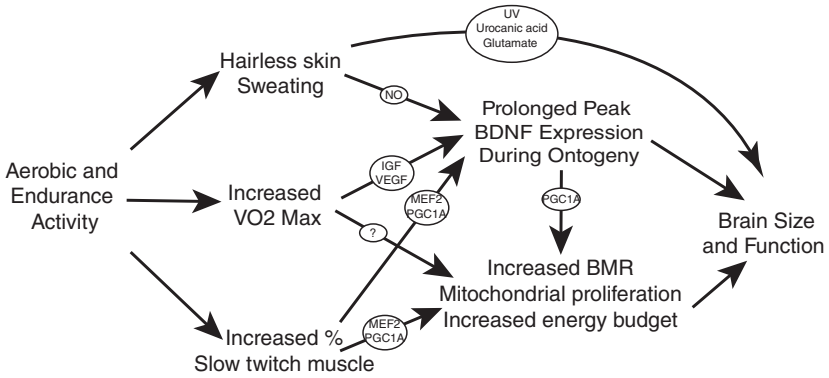

FIGURE 6 Schematic illustration of some of the pathways and interactions among physiological systems that influence BDNF and glutamate synthesis and which contribute to larger brain size and improved function

4.1 | Implications for brain evolution

Our aim in this article is to extend and modify some of the mechanisms identified by Raichlen and Polk (2013). Raichlen and Polk (2013) had argued that selection for endurance running resulted in a systemic upregulation of BDNF (unrelated to exercise) during growth, and that this upregulation contributed to differential brain growth. Here, we modify Raichlen and Polk's model by emphasizing (i) the prolongation of peak BDNF activation (Liu et al., 2012), and (ii) that the selection for endurance running produced changes in muscular, metabolic and integumentary systems which have positive effects on BDNF expression. In this way we provide more detail on the mechanisms underlying brain growth. The evolutionary effects of the muscular/metabolic and integumentary systems on brain growth are different, and require separate treatment.

4.2 | Neural consequences of muscular and metabolic changes

Selection for endurance behavior has resulted in changes to the muscular system and overall energy budgets, mediated in part by PGC-1α. PGC-1α is involved in mitochondrial proliferation, is a genetic correlate of $VO_{2\ max}$ (Figure 3), modulates lipid and glucose metabolism (Lin et al., 2005), and has direct interactions with BDNF. Thus, regulation of PGC-1α expression may be one of the important mechanistic links in this relationship. PGC-1α is also involved in the determining fiber type in muscles.

Several explanations for hominin brain growth are tied to energy budgets. Aiello and Wheeler (1995) proposed an energetic trade-off between organ systems whereby decreases in gut size enabled energy reallocation to permit increased brain growth. Although some

TABLE 1 Explanation of abbreviations

Abbreviation	Description	Relevance
BDNF	Brain-derived neurotrophic factor	Neurotrophic protein encoded by the *BDNF* gene. Produced in the brain and periphery. Important for neural growth and plasticity. Central modulator of systemic energy homeostasis.
CMAH	Cytidine monophosphate-N-acetylneuraminic acid hydroxylase-like protein	Gene encoding an enzyme needed to synthesize N-glycolylneuraminic acid. Mutated to an inactive form in human lineage. Implicated in the evolution of human endurance capability.
CPC	Cortical progenitor cells	Type of cell that proliferates leading to cortical growth and development.
CVR	Cutaneous vasodilatory response	Temperature-mediated dilation of blood vessels in the skin. Involved in thermoregulatory response.
FNDC5	Fibronectin type III domain-containing protein 5, the precursor of irisin, is a protein that is encoded by the *FNDC5* gene	Irisin is secreted in muscles in response to exercise. Related to PGC-1α function.
MEF2	Myocyte enhancer factors	Family of transcription factors (A–D) with prominent role in regulating muscle development. Has various roles in neural development.
NO	Nitric oxide	Signaling molecule in many physiological systems.
NOS	Nitric oxide synthase	Family of enzymes catalyzing the production of NO.
PGC-1α	Peroxisome proliferator-activated receptor γ coactivator 1α [protein]	Transcriptional coactivator that regulates genes involved in energy metabolism. Master regulator of mitochondrial biogenesis. Involved in energy metabolism and determination of muscle fiber type.
PPARGC1A	Peroxisome proliferator-activated receptor γ coactivator 1α [gene]	Gene encoding PGC-1α. Also known as human accelerated region 20.
TrkB	Tropomysin receptor kinase B	Tyrosine kinase receptor with high affinity for BDNF.
UCA	Urocanic acid	A molecule in the skin that can act as endogenous sunscreen. Involved in T-cell regulation. Promotes glutamate synthesis in the brain.

anatomical evidence is consistent with such a tradeoff in primates (Aiello and Wheeler, 1995), this hypothesis assumes that the total energy expenditure is constrained among anthropoid primates. Navarrete et al. (2011) did not find support for such a tradeoff across a larger mammalian sample. Rather, these authors suggested that human encephalization was related to tradeoffs in adipose storage, which entailed a more stabilized energy input and redirection of energy to the brain from locomotion, growth, and reproduction (see also Bozek et al., 2015; Isler & van Schaik, 2012). Though intriguing, tradeoff models assume that energy budgets are constrained among anthropoid primates. Work by Pontzer and colleagues (Pontzer, 2015; Pontzer et al., 2016), however, shows that total energy expenditure is increased in humans relative to other primates, casting doubt on the need for tradeoff models in explaining human brain evolution. Behavioral innovations, such as cooking, and changes in food quality (Carmody & Wrangham, 2009; Fish & Lockwood, 2003) may have facilitated the acquisition of a higher energy budget, but the mechanisms tying these changes to encephalization have not previously been specified.

We argue here that the selection for endurance capacity resulted in altered activity levels of PGC-1α and MEF2 and result in increased energy budget, altered mitochondrial dynamics and greater percentage of ST muscle composition in humans, relative to earlier hominins. The consequences for brain growth are twofold: first, more energy is available for brain growth throughout ontogeny, and second, changes in PGC-1α and MEF2 have direct effects on BDNF activity. The effects on brain growth would have been pronounced early in postnatal life when locomotor demands are relatively low (consistent with Navarrete et al. [2011]) and would continue throughout ontogeny. Changes in human adiposity and its relation to brain growth, as stressed by Isler and van Schaick (2012) and others, may be also underpinned partly by the peroxisome proliferator-activated receptor family's role in peripheral adipose storage (Jones et al., 2005) and lipid metabolism in the brain (Kainu, Wikström, Gustafsson, & Pelto-Huikko, 1994; Sarruf et al., 2009).Whether altered PGC-1α activity contributes to the prolongation of peak BDNF and MEF2 expression noted by Liu et al. (2012) has not been tested, but this prolonged peak expression of BDNF corresponds to the prolongation of human versus chimpanzee brain growth (Bogin, 1997; Leigh, 2004). In the hominin fossil record, this pattern of prolonged brain growth appears to have evolved after *H. erectus* (Leigh, 2012), perhaps corresponding to the timing of alteration to the expression patterns.

The fact that mitochondrial dynamics have been shown to be important regulators of energy expenditure (Liesa & Shirihai, 2013) suggests that future comparative work among hominid species may be productive. For example, while mitochondrial dynamics have been implicated in mesenchymal, hematopoietic, and other stem cell systems, there is only limited work on how mitochondrial dynamics influence neural differentiation (see Khacho & Slack, 2018, and references therein), with evidence associating an increase in oxidative metabolism with progressive differentiation of neural cell types throughout development.

4.3 | Neural consequences of integumentary changes

Many evolutionary changes to the human integumentary system have been well documented (Jablonski, 2004). Selection for endurance activity in warm climates has altered the thermoregulatory ability of the skin by reducing hair covering, enabling more UV exposure and evaporative sweating (Wheeler, 1984, 1991; Carrier, 1984; Ruxton & Wilkinson, 2011). These changes have two consequences for brain function and possibly for growth. First, UV exposure has been shown to increase glutamate synthesis in the brain, thereby promoting improvements in cognitive function (Zhu et al., 2018). We are not yet aware of evidence that would mechanistically link this benefit to brain size.

The second potential benefit is related to NO produced through the CVR. NO is necessary for expression of the CVR and is a known upregulator of BDNF. We include discussion of this mechanism because of its potential contribution to interspecific differences in brain size that likely accompanied the evolution of hairlessness in hot climates. In such environments, where NO production is higher, there may be neural benefits. These benefits may not extend to explaining interpopulational variation in human brain size. For example this model would suggest that brain size might be larger in warmer climates. In contrast, Beals et al. (1984) demonstrate cranial capacity is larger in colder climates, though they did not control for population histories. In a combined morphological and population genetic study, Roseman (2004) found that most interpopulational variation in cranial shape was attributable to drift, and in only one of the samples was deviation from drift noted. That is, a Siberian population was notably brachycephalic, a feature attributed to temperature-based selection (though the authors were careful to point out that similar shape differences were not observed in Inuit crania). While these temperature-mediated differences may not explain variation in overall brain size, there may still be local brain effects or alterations in vascularization, but these remain to be demonstrated.

5 | CONCLUSIONS

Our review further corroborates Raichlen and Polk's (2013) contention that selection acting on noncognitive phenotypes can have effects on brain development and function. More specifically, the changes wrought by selection acting on endurance and aerobic capabilities early in the human lineage have had wide-ranging consequences (Figure 6). We contend that selection favoring endurance activity during human evolution produced changes in muscle physiology and energy budgets mediated by *PPARGC1A* and *MEF2* families of genes. These changes resulted in prolonged high expression of these genes resulting in prolonged high expression of BDNF, compared with other species (Liu et al., 2012), and these changes would have been manifest regardless of activity level during ontogeny. We also argue that the evolution of hairlessness and thermoregulatory changes in the skin have neural consequences via both UV-promoted synthesis of glutamate, and by regulatory effects of NO on BDNF. Taken together, these regulatory pathways appear to have evolved as downstream consequences of the need for endurance activity in warm

climates. We regard these ideas as hypotheses that move toward understanding the mechanistic bases for changes in brain structure and growth, and we acknowledge that this review is far from comprehensive. There are many avenues for testing these and related hypotheses.

For example, while we focus on BDNF, there are other genes that are known to affect brain expansion. Two examples are *ARHGAP11B* and *HARE5*, which arose in hominins before the divergence of Denisovans, Neanderthals, and humans (Florio et al., 2015, 2017; Boyd et al., 2015). In transgenic mouse models, expression of either gene significantly expands the neocortex by amplifying basal progenitor cells (Florio et al., 2015). Mechanistic connections between BDNF and these genes have not been the specific focus of investigation. However, because BDNF acts to promote progenitor survival, some interaction seems plausible.

Many other mechanistic questions deserve further attention. For example, how does the brain receive and transduce information about increased aerobic capacity? Rats with high aerobic capacity have higher muscle capillary density (perhaps due to upregulated VEGF) and higher baseline levels of IGF-1. Work by Monnier et al. (2017) showed that vascular endothelial cells in the brain produce more BDNF than previously thought. They also found that exercise increased BDNF in the endothelial cells, not just in neurons. Interconnections between BDNF and VEGF have been noted by Cotman et al. (2007), and presumably changes in vascular function are necessary for neurogenic responses (Jin et al., 2002). Similarly, this review focuses on levels of BDNF in the brain and circulatory system.

Humans' response to BDNF might also be a product of greater BDNF sensitivity, perhaps by greater BDNF receptor density. We are unaware of comparative data among humans and great apes that could test this hypothesis. In addition, while positive selection on BDNF has been demonstrated in mammals compared with other vertebrates (Tettamanti et al., 2010), similar tests for selection need to be performed within mammals in order to test hypotheses relating this factor to differential brain growth during human evolution. Finally, while some preliminary work has highlighted the influence of mitochondrial dynamics and associated metabolic processes on neural proliferation in mice (Beckervordersandforth et al., 2017; Khacho & Slack, 2018), comparative work in this area is necessary.

Finally, recent work has suggested that human endurance capacity may be explained largely by a genetic change affecting *CMAH* (Okerblom et al., 2018). While such singular changes with wide-ranging implications are tantalizing, we believe there is value in linking these changes to downstream physiological and genetic mechanisms in order to increase the explanatory power. We look forward to studies evaluating functional linkages between *CMAH* and some of the mechanisms identified here (Figure 6).

ACKNOWLEDGMENTS

The authors wish to thank Rebecca Stumpf, members of the Evolutionary Biomechanics lab, two anonymous reviewers and *Yearbook* editors for critical and constructive feedback. Jan Troutt produced the artwork for Figure 5. This research was supported by National Science Foundation BCS-1638756. The authors have no conflicts of interest to report.

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How to cite this article: Hill T, Polk JD. BDNF, endurance activity, and mechanisms underlying the evolution of hominin brains. *Am J Phys Anthropol*. 2019;168:S67:47–62. https://onlinelibrary.wiley.com/doi/10.1002/ajpa.23762